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Avian influenza: assessing the pandemic threat

World Health Organization

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Foreword

Influenza pandemics are associated with high morbidity, excess mortality, and social and economic disruption. There were three such pandemics in the twentieth century: in 1918, 1957, and 1968. During 2004, the world moved closer to a further pandemic than it has been at any time since 1968.

In the past, pandemics have announced themselves with a sudden explosion of cases which took the world by surprise. This time, we have been given a clear warning. During 2004, large parts of Asia experienced unprecedented outbreaks of highly pathogenic avian influenza, caused by the H5N1 virus, in poultry. The virus crossed the species barrier to infect humans, with a high rate of mortality. Monitoring of the evolving situation, coordinated by WHO, has produced many signs that a pandemic may be imminent. This time, the world has an opportunity to defend itself against a virus with pandemic potential before it strikes.

Preparedness for a pandemic presents a dilemma: what priority should be given to an unpredictable but potentially catastrophic event, when many existing and urgent health needs remain unmet? In such a situation, it is useful to put together all the known facts that can help us to see where we stand, what can happen, and what must be done. That is the purpose of this publication.

The H5N1 virus has given us not only a clear warning but time to enhance preparedness. During 2004, concern about the threat of a pandemic set in motion a number of activities, coordinated by WHO, that are leaving the world better prepared for the next pandemic, whenever it occurs and whichever virus causes it. Nonetheless, our highly mobile and interconnected world remains extremely vulnerable. No one can say whether the present situation will turn out to be another narrow escape or the prelude to the first pandemic of the 21st century. Should the latter event occur, we must not be caught unprepared.

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Introduction

This publication evaluates the present pandemic threat on the basis of what we know about pandemics, influenza A viruses, and the H5N1 virus in particular. It draws together some current facts and figures, evidence from the past, and some best-guess speculations useful in assessing the present situation and understanding its multiple implications for human health. Basic information on human cases detected to date is set out in tabular form.

The publication has four chapters. Chapter 1 traces the evolution of the outbreaks of highly pathogenic H5N1 avian influenza, in humans and poultry, during 2004. For avian influenza viruses, this was an historically unprecedented year. Never before had so many countries been so widely affected by avian influenza in poultry in its most deadly form. Never before had any avian influenza virus caused such extremely high fatality in humans, taking its heaviest toll on children and young adults in the prime of life. The chapter also describes some disturbing new findings about the evolution of the virus that suggest a deepening threat. These changes have made surveillance for human cases, especially in rural areas, far more difficult.

Chapter 2 looks at past pandemics as a basis for assessing what may be on its way. It gives particular attention to patterns of international spread, population groups at special risk, and the effectiveness of the different public health and medical interventions that were applied. One conclusion is clear: past pandemics have been as unpredictable as the viruses that caused them. While the number of deaths has varied greatly, these events do have two consistent features. First, they always cause a sudden and sharp increase in the need for medical care, and this has great potential to overwhelm health services. Second, they always spread very rapidly to every part of the world.

The threat of H5N1 to human health, both immediately and in the future, is closely linked to the outbreaks of highly pathogenic avian influenza in poultry, as described in chapter 3. This chapter explains the disease and summarizes the history of past outbreaks in order to place the present situation in perspective and assess its implications for public health. In poultry, the H5N1 outbreaks have been a catastrophe for agriculture. They have affected the very backbone of subsistence farming in rural areas where large numbers of people depend on poultry for livelihood and food, and this, too, is of public health concern.

Against this background, the final chapter looks at the many activities set in motion during 2004 to improve pandemic preparedness and prevent further human cases. These activities range from intensified surveillance and faster reporting, through molecular characterization of viruses, to work on the development of a pandemic vaccine. WHO, including its outbreak response teams and staff in regional and country offices, has contributed directly to all these activities and helped them to move forward. The chapter also describes the role of antiviral drugs before and at the start of a pandemic, and provides advice on the use of non-medical interventions, such as quarantine and travel restrictions. On the positive side, the chapter shows how concern about the pandemic threat is leaving the world permanently better prepared to respond to any future pandemic caused by any influenza virus.

1 The H5N1 outbreaks in 2004: a pandemic in waiting?

Since 1959, human infections with avian influenza viruses have occurred on only 11 occasions. Of these, 6 have been documented since 2003.

At some unknown time prior to 1997, the H5N1 strain of avian influenza virus began circulating in the poultry populations of parts of Asia, quietly establishing itself. Like other avian viruses of the H5 and H7 subtypes, H5N1 initially caused only mild disease with symptoms, such as ruffled feathers and reduced egg production, that escaped detection. After months of circulation in chickens, the virus mutated to a highly pathogenic form that could kill chickens within 48 hours, with a mortality approaching 100%. The virus first erupted in its highly pathogenic form in 1997, but did not appear again. Then, towards the end of 2003, H5N1 suddenly became highly and widely visible.

The first report of something unusual came from the Republic of Korea in mid-December 2003. Veterinarians were concerned about the sudden death of large numbers of chickens at a commercial poultry farm near the capital city of Seoul. On 12 December, the country's chief veterinary officer sent an emergency report to the World Organisation for Animal Health (OIE) in Paris. The initial diagnosis was highly pathogenic avian influenza – a disease never before seen in the country. Both the origin of infection and mode of spread were listed as "unknown". By 16 December, the disease had spread to another two farms, and laboratory tests had identified the causative agent: the H5N1 strain.

That finding grabbed the immediate attention of health experts. Of all viruses in the vast avian influenza pool, H5N1 is of particular concern for human health for two reasons. First, H5N1, though strictly an avian pathogen, has a documented ability to pass directly from birds to humans. Second, once in humans, H5N1 causes severe disease with very high mortality. These two features combine to make H5N1 of concern for a third and greater reason: its potential to ignite an especially severe pandemic.

Cumulative human cases of avian influenza since 1959

Virus	Cases	Deaths
H5N1	70	**43**
all other avian influenza viruses	101	**1**

The 1997 outbreak in Hong Kong SAR

The first documented occurrence of H5N1 infection in humans involved 18 cases, of which 6 were fatal. Ages ranged from 1 to 60 years, with more than half of cases occurring in children aged 12 years or younger.

In severe cases, disease features included primary viral pneumonia and multiple organ failure.

Cases occurred in two waves: 1 case in May and 17 during November and December.

Molecular studies showed that viruses from humans and poultry were virtually identical, indicating that the virus jumped directly from birds to humans. Most human cases could be traced to direct contact with poultry.

The absence of disease in two high-exposure groups – poultry workers and cullers – indicates that H5N1 did not cross easily from birds to humans.

Antibodies to the H5 virus subtype were found in blood samples taken from family members and health care workers in close contact with patients. Very limited human-to-human transmission may have occurred, but was of low efficiency and did not cause symptoms or disease.

The outbreak ended after all of Hong Kong SAR's 1.5 million poultry were slaughtered within three days (29–31 December).

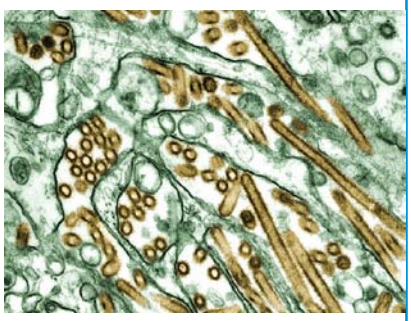
Historically, human infections with avian influenza viruses have been extremely rare. Most of these viruses have caused only mild illness in humans, often in the form of viral conjunctivitis, followed by full recovery. H5N1 has been the exception. In the first documented instance of human infection, the virus caused 18 cases, of which 6 were fatal, in China, Hong Kong Special Administrative Region (Hong Kong SAR)* in 1997. The cases coincided with outbreaks of highly pathogenic H5N1 in poultry on farms and in live markets. Many experts believe that the destruction, within three days, of Hong Kong SAR's entire poultry population of 1.5 million birds averted a pandemic by immediately removing opportunities for further human exposure. That action was subsequently vindicated by evidence that the virus had begun to mutate in a dangerous way.

A striking feature of the Hong Kong SAR outbreak was the presence of primary viral pneumonia in severe cases. When pneumonia occurs in influenza patients, it is usually a complication caused by a secondary bacterial infection. In the H5N1 cases, pneumonia was directly caused by the virus, did not respond to antibiotics, and was frequently rapidly fatal. With one exception, none of these patients had underlying disorders that could explain the severe course of the disease.

In February 2003, H5N1 again caused human cases, this time in a Hong Kong SAR family with a recent travel history to southern China. The 33-year-old father died, but his 9-year-old son recovered. A second child, an 8-year-old girl, died of a severe respiratory illness in mainland China; she was not tested and the cause of her illness will never be known. That small but ominous event convinced many experts that the virus was still circulating in mainland China – a part of the world long considered the epicentre of influenza virus activity and the birthplace of pandemics.

The Hong Kong SAR experience of 1997 clearly demonstrated the pandemic potential of H5N1 and made it a prime suspect to watch. It also altered understanding of how a new pandemic virus might emerge. Apart from being highly unstable and prone to small mutational errors, influenza viruses have a segmented genome, consisting of eight genes, that allows easy swapping of genetic material – like the shuffling of cards – when a host is coinfected

* References to Hong Kong SAR include mentions of the territory before 1997.



H5N1: a virus with proven pandemic potential
(Source: CDC Public Health Image Library).

with two different viruses (Box 1). The pandemics of 1957 and 1968 are known to have been caused by new viruses, containing both human and avian genes, that emerged following a reassortment event in which viruses from the two species coinfected the same cell and exchanged genes. Prior to 1997, pigs were thought to be the obligatory mixing vessel for reassortment of viruses, as they possess receptors for both avian and human influenza viruses on the cells of their respiratory tract. The Hong Kong SAR event, however, demonstrated that humans could be directly infected with a purely avian influenza virus, such as H5N1, and thus also serve as the mixing vessel for the exchange of virus genes. That finding gave human infections with H5N1 added significance as a warning signal that a pandemic might be imminent.

A rapid escalation of concern

5 January 2004
Viet Nam alerts WHO to an unusual cluster of very severe respiratory disease in children at a hospital in Hanoi.

8 January
H5N1 is found in dead chickens in the southern part of Viet Nam.

11 January
H5N1 – a purely avian virus – is detected in samples from fatal cases in Hanoi.

12 January
Japan announces detection of H5N1 in poultry, becoming the third affected country in Asia.

14 January
WHO sends an emergency alert, placing its partners in the Global Outbreak Alert and Response Network (GOARN) on stand-by.

19 January
The first GOARN team arrives in Viet Nam, where five fatal cases have now been confirmed.

23 January
Thailand reports H5N1 in humans and poultry.

High alert

In January 2004, WHO officials were understandably on high alert for any signs that H5N1 might again cross the species barrier to cause disease in humans. On 5 January, Vietnamese health authorities informed the WHO office in Hanoi of an unusual cluster of severe respiratory disease in 11 previously healthy children hospitalized in Hanoi. Of these patients, 7 had died and 2 were in critical condition. Treatment with antibiotics produced no response, and a viral cause was suspected. Infection with the SARS virus was considered but did not seem likely. For unknown reasons, SARS tended to spare children, rarely causing severe illness, and was never considered a paediatric disease. WHO was asked to assist in the Hanoi investigation, and arrangements were made for testing of patient specimens at WHO reference laboratories.

Concern intensified on 8 January, when Viet Nam confirmed that large die-offs of poultry at two farms in a southern province were caused by highly pathogenic H5N1. At that time, the northern part of the country was not known to be experiencing outbreaks in poultry, and no epidemiological evidence suggested a link between the unidentified disease in Hanoi and exposure to poultry infected with H5N1. Nonetheless, the level of suspicion was high and concern remained great.

Box 1. **Influenza A viruses: sloppy, capricious, and promiscuous**

Influenza viruses are grouped into three types, designated A, B, and C. Viruses of the C types are common but usually cause no symptoms or only very mild respiratory illness. They are not considered of public health concern. Type B viruses cause sporadic outbreaks of more severe respiratory disease, particularly among young children in school settings. Both B and C viruses are essentially human viruses; C viruses are stable, but A and B viruses are prone to mutation.

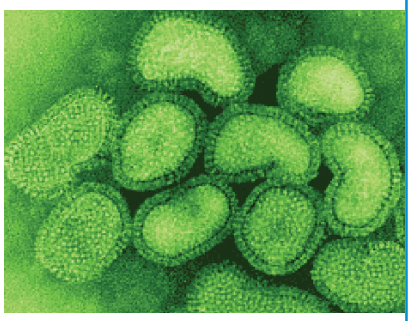
Of greatest concern are the influenza A viruses. They have characteristics that make influenza A one of the most worrisome of all the well-established infectious diseases. These viruses mutate much more rapidly than type B viruses, and this gives them great flexibility. In addition to humans, they infect pigs, horses, sea mammals, and birds. They have a large number of subtypes, all of which are maintained in aquatic birds, providing a perpetual source of viruses and a huge pool of genetic diversity. As a result of their unique features, influenza A viruses regularly cause seasonal epidemics in humans that take a heavy toll in morbidity and excess mortality, especially when pneumonia is a complication. At recurring yet unpredictable intervals, influenza A viruses cause pandemics.

Scientists describe these viruses as sloppy, capricious, and promiscuous. Their labile and unpredictable nature is notorious. As they lack a proof-reading mechanism, the small errors that occur when the virus copies itself are left undetected and uncorrected. As a result, influenza A viruses undergo constant stepwise changes in their genetic make-up. This strategy, known as antigenic drift, works well as a short-term survival tactic for the virus: the speed with which slight variations develop keeps populations susceptible to infection. Though small, the changes are sufficient to evade the defences of the immune system. Populations protected, whether because of previous infection or vaccination, against one virus strain will not be protected when the next slightly different virus arrives. A new vaccine* must therefore be produced for each winter season in temperate climates, when epidemics of influenza almost always occur. Influenza viruses circulate year-round in tropical and subtropical areas.

As yet another feature, the genetic content of these viruses is neatly segmented into eight genes. This facilitates the most greatly feared event: the swapping of gene segments during coinfection with human and avian influenza viruses, creating a new virus subtype that will be entirely or largely unfamiliar to the human immune system. If this new "hybrid" virus contains the right mix of genes, causing severe disease and allowing easy and sustainable human-to-human transmission, it will ignite a pandemic. This strategy, known as antigenic shift, works well as a long-term survival tactic: immunologically, a new virus subtype starts from scratch and is guaranteed a very large population of susceptible hosts.

Pandemics are rare but recurring events, invariably associated with great morbidity, significant mortality, and considerable social and economic disruption. Population vulnerability, combined with the highly contagious nature of influenza viruses, means that all parts of the world are rapidly affected, usually within less than a year.

* *Vaccines for seasonal influenza are trivalent vaccines. They confer protection against two influenza A viruses and one influenza B virus circulating in a given season.*



Influenza viruses are highly unstable, genetically labile, and well adapted to elude host defences.

The situation altered dramatically on 11 January, when a WHO reference laboratory announced detection of H5N1 in specimens from 2 of the fatal cases in Hanoi. Confirmation of H5N1 in a third fatal case was received the following day. That same day, in another ominous development, Japan reported a large outbreak of highly pathogenic avian influenza, caused by the H5N1 strain, at a single poultry farm in Kyoto prefecture. In Viet Nam, the extent of poultry outbreaks was rapidly becoming apparent: within three weeks following the initial report, more than 400 outbreaks were detected throughout the country, affecting at least 3 million poultry. An agricultural nightmare had begun.

The confirmation of human cases gave the outbreaks in poultry a new dimension. They were now a health threat to populations in affected countries and, possibly, throughout the world. All prerequisites for the start of a pandemic had been met save one, namely the onset of efficient human-to-human transmission. Should the virus improve its transmissibility, everyone in the world would be vulnerable to infection by a pathogen – passed along by a cough or a sneeze – entirely foreign to the human immune system.

Prerequisites for the start of a pandemic

Research has identified three prerequisites for the start of a pandemic.

1. A novel virus subtype must emerge to which the general population will have no or little immunity.
2. The new virus must be able to replicate in humans and cause serious illness.
3. The new virus must be efficiently transmitted from one human to another; efficient human-to-human transmission is expressed as sustained chains of transmission causing community-wide outbreaks.

Pandemic alert: the response plan

Fully aware of these risks, WHO activated its pandemic preparedness plan, alerted its network laboratories, and placed response teams on standby. WHO also mapped out a response plan with three objectives: to avert a pandemic, to control the outbreak in humans and prevent further cases, and to conduct the research needed to monitor the situation and improve preparedness, including the immediate development of a pandemic vaccine.

To meet the first two objectives, the foremost need was to reduce opportunities for human exposure by eliminating the virus from its poultry host. Fortunately, the measures for doing so were being vigorously implemented in line with recommendations issued by OIE and the Food and Agricultural Organization of the United Nations (FAO). These called for the immediate culling of infected or exposed birds, quarantine and disinfection of farms, control of animal movements, and implementation of strict biosecurity

The naming of influenza viruses

Influenza A viruses get their names from two sets of protein spikes that jut from the outer surface of the virus. The haemagluttinin, or HA, spike governs virus binding and entry into cells, where copies of the virus are produced. There are 15 HA subtypes, designated H1 to H15. Immunity to an HA subtype – whether conferred by vaccination or previous exposure to that subtype – protects against infection, but only for that subtype.

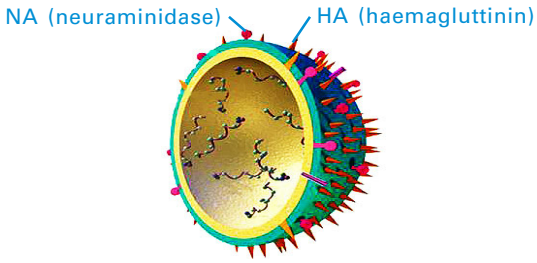
The neuraminidase, or NA, spike governs the release of newly formed virus from infected cells into the host's body. There are 9 NA subtypes, designated N1 to N9. Immunity to an NA subtype reduces the amount of virus released from a cell, resulting in less severe disease.

All 15 HA subtypes and 9 NA subtypes have been detected in free-flying birds. They provide a huge – and highly mobile – pool of genetic diversity.

An individual virus strain is identified by the subtypes of HA and NA protein spikes on its surface. It is named by the letters H and N, each followed by the number of the subtype.

For pandemics, a novel HA subtype is decisive, as it determines population susceptibility. To date, only subtypes H1, H2, and H3 are known to have circulated in humans for at least a century.

As a virus from the H5 subtype will be foreign to the immune system of everyone alive today, vulnerability to an H5N1-like pandemic virus would be universal.



measures on farms. WHO added to these measures by recommending that poultry cullers wear protective clothing and take antiviral drugs as a precaution. Vaccination against normal seasonal influenza was also recommended as a way to reduce chances that this high-risk group might be coinfected with an avian and a human virus, this giving the viruses an opportunity to exchange genes.

In pursuing the third objective, researchers could draw on a growing body of knowledge about pandemic viruses in general and H5N1 in particular that arose following the close call of 1997. This intensified research had done much to characterize H5N1 at the molecular level, track its evolution in avian species, improve understanding of its pathogenicity in humans, and define its pandemic potential. By the third week of January, laboratories in the influenza network had determined that the 2004 virus had mutated considerably since the Hong Kong SAR cases in 1997 and 2003. Work done to prepare a vaccine against an H5N1-like pandemic virus would have to start again from scratch. H5N1 viruses from 2004 also showed resistance to one of only two classes of antiviral drugs available to prevent severe disease. Fear increased that, should a pandemic begin quickly, the world would be caught short with little in the way of medical tools to fight back.

The next major blow came on 23 January, when Thailand announced its first human cases of H5N1 in two young boys. A large outbreak at a poultry farm, affecting nearly 70 000 birds, was announced on the same day. During the remaining days of January, a small but steady number of human cases, most of which were fatal, continued to be reported from both Viet Nam and Thailand. These cases occurred against a backdrop of poultry outbreaks that seemed to worsen as each day passed. During the last week of January, Thailand reported 156 outbreaks in 32 provinces affecting 11 million birds.

Response teams for the WHO Global Outbreak Alert and Response Network (GOARN) were immediately despatched to both Viet Nam and Thailand to support the work of local health officials. WHO also issued a series of guidelines to facilitate heightened surveillance and case detection, laboratory diagnosis according to international standards, and infection control to prevent amplification of cases in health care settings.

Countries with outbreaks largely confined to commercial farms faced the best prospects for successful control.

Among the January cases, two sisters in Viet Nam became the focus of intense investigation when evidence suggested they might represent the first instance of human-to-human transmission (Box 2). While no firm conclusions could be reached, the possibility could not be ruled out that the women, both of whom died from confirmed H5N1 infection, acquired the virus from their brother, who also suffered from a fatal respiratory infection but was not tested.

Outbreaks in poultry: historically unprecedented

Prior to the outbreaks of 2004, highly pathogenic avian influenza was considered a rare disease in poultry.

Near the end of January, the situation in poultry exploded. Outbreaks in the Republic of Korea, Viet Nam, Japan, and Thailand were followed by reports of the same disease in Cambodia, Lao People's Democratic Republic, Indonesia, and China. Most of these countries had never before experienced outbreaks of highly pathogenic avian influenza caused by any strain.

Of these countries, Japan and the Republic of Korea were the most fortunate, as their outbreaks remained largely confined to commercial farms where outbreaks are readily detected and conditions are compatible with rapid implementation of control measures. Thailand and Viet Nam were the most severely affected; outbreaks rapidly extended to all parts of both countries, including large rural areas where nearly every household kept a flock of free-ranging chickens and ducks. China experienced outbreaks in more than half of its 31 provinces and municipalities. In that country, home to more than 13 billion chickens, of which 60% are raised on small farms, compulsory vaccination was introduced to supplement standard control measures. From the outset, neither Cambodia nor Lao People's Democratic Republic was in a position to conduct similarly aggressive control campaigns, as neither country had sufficient surveillance systems or resources. In Indonesia, health authorities and facilities were fully occupied by a large outbreak of dengue fever that began at the start of January. That outbreak, which continued through April, caused more than 58 000 cases and 650 deaths, and left few resources in reserve to deal with an animal disease.

More than 120 million birds died or were destroyed within three months. (Sources, top: WHO/ Huang Liang-China Daily; bottom: AP)

By the start of February, it was clear that the H5N1 outbreaks in poultry were historically unprecedented. Prior to the Asian outbreaks, highly pathogenic avian influenza was considered a rare disease. Beginning in 1959, when the disease was first recognized, only 21 outbreaks occurred worldwide prior to 2004, with the majority in Europe and North America. Of these, only seven resulted in significant spread to numerous farms, and only one spread to other countries.

Never before had highly pathogenic avian influenza caused outbreaks in so many countries at once. Never before had the disease spread so widely and rapidly to affect such huge geographical areas. Never before had it caused such enormous consequences for agriculture – from large commercial farms to the roots of rural subsistence agriculture. In several affected countries, 50% to 80% of poultry are raised in small rural households where they provide a source of income, around 30% of total dietary protein, and an "insurance policy" for raising cash when medicines need to be purchased.

In an historically unprecedented situation, anything can happen. During the second phase, many things did.

In the Asian outbreaks, more than 120 million birds died or were destroyed within three months. That figure is higher than the combined total from all previous large outbreaks of highly pathogenic avian influenza recorded throughout the world over four decades.

The massive control efforts had an impact, and the outbreaks declined sharply during March except in Thailand, where sporadic outbreaks continued to be reported through April. Predictably, new human cases dwindled then ceased, with the last occurring in mid-March in Viet Nam. From January through March, Viet Nam and Thailand together reported 35 cases, of which 24 were fatal (Tables 1 and 2). These figures made the outbreak in humans almost twice the size of that in 1997, and far more deadly.

In an historically unprecedented situation involving a virus as mutable as influenza, anything can happen. And, as the second phase would prove, many things did.

Thousands of poultry workers, often inadequately protected, experienced intense exposures to the virus, giving it ample opportunities to reassort (Source: AP).

The second phase: more cases – and more surprises from the virus

Virus activity for H5N1 is known to peak from November through March. As spring turned to summer, the worst seemed to be over. Two questions hung in the air. First, had the massive control efforts managed to eliminate the virus? Past experience argued strongly against that prospect. Even under far more favourable circumstances, with outbreaks concentrated in a few commercial farms in a small geographical area, complete elimination of the virus typically required two to three years. More likely, H5N1 was merely quiescent, or possibly still active in rural areas where deaths in small backyard flocks were likely to escape detection.

The second question was more puzzling: why had H5N1 failed to reassort? It had certainly had ample opportunities to do so. Virological surveillance demonstrated the co-circulation of normal human influenza strains during peak H5N1 activity. Many thousands of workers, often inadequately protected, had experienced intense exposures during culling operations. The answer might lie in sheer statistical luck – not many human cases had been reported. Many experts believed, however, that numerous other cases, too mild to be detected, were almost certainly occurring, thus expanding opportunities for coinfections.

Though the outbreaks in poultry were much smaller, human cases again occurred.

Events beginning in July answered the first question decisively and rendered the second temporarily irrelevant. Fresh outbreaks were reported in Cambodia, China, Indonesia, Thailand, and Viet Nam. In late August, Malaysia – a country spared during the first wave – reported its first poultry outbreaks. Compared with the first wave, these outbreaks were much smaller, affecting less than 1 million poultry during the summer and autumn of 2004. They also proved remarkably tenacious. Several countries, on the verge of declaring themselves free of H5N1 outbreaks, suffered setbacks when the virus cropped up in yet another flock or farm.

Despite the much smaller areas and numbers of birds affected, human cases again occurred. From August through October, 9 cases, of which 8 were fatal, were reported in Thailand (5) and Viet Nam (4). Most cases occurred in rural areas, suggesting a community-wide threat to health in large and remote areas. In

The July 2004 outbreaks in poultry

Country	No. of birds affected[a]
Cambodia	23
China	8 000
Indonesia	2 500
Thailand	123 000
Viet Nam	17 000

[a] As reported to OIE.

Recent events indicate that the virus is expanding its mammalian host range. In October 2004, H5N1 caused a large and deadly outbreak in captive tigers – a species not considered susceptible to disease from any influenza A virus.

September, Thailand reported its first probable case of human-to-human transmission in a family cluster. That finding initiated a massive door-to-door search, involving around 1 million volunteers. No further clusters suggesting continuing transmission were detected.

The newly reported cases brought the total since January, in the two countries, to 44, of which 32 were fatal. When these cases are viewed together, two features are striking: the overwhelming concentration of cases in previously healthy children and young adults, and the very high mortality. No scientific explanation for this unusual disease pattern is presently available. Nor is it possible to calculate a reliable case-fatality rate, as mildly symptomatic disease may be occurring in the community, yet escape detection.

Although the second wave of outbreaks has been far less conspicuous, it has demonstrated several unusual features. These suggest that the virus may be evolving in ways that increasingly favour the start of a pandemic.

Although the second wave of outbreaks has been far less conspicuous in the numbers of humans and animals affected, it has demonstrated several unusual features. These features, confirmed by findings from recent epidemiological and laboratory studies, suggest that the virus may be evolving in ways that increasingly favour the start of a pandemic.

Evidence strongly indicates that H5N1 is now endemic in parts of Asia, having established a permanent ecological niche in poultry. The risk of further human cases will continue, as will opportunities for a pandemic virus to emerge. Studies comparing virus samples over time show that H5N1 has become progressively more pathogenic in poultry and in the mammalian mouse model, and is now hardier than in the past, surviving several days longer in the environment. Evidence further suggests that H5N1 is expanding its mammalian host range. For example, the virus has recently been shown to cause severe disease and deaths in species, including experimentally infected domestic cats and naturally infected captive tigers, not previously considered susceptible to disease caused by any influenza A virus. The outbreak in tigers, which began on 11 October in Thailand, had a second disturbing feature. Altogether, 147 tigers in a population of 418 developed high fevers, usually progressing to severe pneumonia, as a result of H5N1 infection. Preliminary investigation found no evidence of tiger-to-tiger transmission. As infection was linked to the feeding of chicken carcasses, the amount of infected chicken moving in the food supply must have been great to have caused disease in so many large animals.

New evidence suggests that domestic ducks are now excreting H5N1 in its highly lethal form without showing signs of illness. This "silent" role of domestic ducks may help explain why some recent human cases cannot be linked to contact with diseased poultry.

Another surprising finding is the detection of H5N1, in its highly pathogenic form, in dead migratory birds. Wild waterfowl are the natural reservoir of all influenza A viruses and have historically carried low-pathogenic viruses, in evolutionary equilibrium, without showing symptoms or succumbing to disease. Although more evidence is needed, the finding suggests that the role of migratory waterfowl in the evolution and maintenance of highly pathogenic H5N1 may be changing. The international threat from infected wild birds was vividly demonstrated in mid-October, when airport authorities in Belgium detected two smuggled mountain hawk eagles carried on a flight from Thailand. Both birds tested positive for H5N1 in its highly pathogenic form.

Another disturbing finding is the detection of H5N1 in dead migratory birds. Wild waterfowl are the natural reservoir of all influenza A viruses and do not normally develop any symptoms.

Of greater concern, asymptomatic domestic ducks have recently been shown experimentally to excrete H5N1 in its highly pathogenic form, suggesting an important silent role in maintaining transmission. As these ducks can excrete large quantities of lethal virus without the warning signal of visible illness, it has become difficult to give rural residents realistic advice on how to avoid exposure. The role of domestic ducks may help to explain why several recent human cases could not be traced to contact with diseased poultry. It is also highly likely that apparently healthy ducks play a role in maintaining transmission by silently seeding outbreaks in other poultry.

The present concentration of poultry outbreaks in rural areas, where most households maintain free-ranging flocks and ducks and chickens mingle freely, is of particular concern, especially as many households depend on these birds for income and food. Such outbreaks may escape detection, are difficult to control, and increase the likelihood of human exposures, which may occur when children play in areas shared by poultry or when families slaughter or prepare birds for consumption.

Taken together, these changes in the ecology of the disease and behaviour of the virus have created multiple opportunities for a pandemic virus to emerge. No one knows whether the present window of opportunity to intensify preparedness will remain open or close abruptly. Experts readily agree, however, that H5N1 has demonstrated considerable pandemic potential. With the virus now endemic, the probability that this potential will be realized has increased.

Changes in 2004: an evolving virus

H5N1 has found a new ecological niche in poultry in parts of Asia.

The virus is now more deadly in poultry and in the mammalian mouse model.

New animals – cats and tigers – are becoming infected for the first time, suggesting the virus is expanding its host range.

Domestic ducks are excreting large quantities of virus without showing symptoms.

Viruses from 2004 survive longer in the environment than viruses from 1997.

The virus is killing at least some wild migratory birds.

These changes have created multiple opportunities for a pandemic virus to emerge.

Assessment of the threat

As virus activity peaks from November through March, further evolution of the situation in early 2005 can be anticipated. In December, Viet Nam reported its largest outbreaks in poultry since September. A third wave of human cases, again in young and previously healthy children and adolescents, began during the last days of December. Good surveillance in the Republic of Korea detected low-pathogenic avian influenza, caused by H5N2, in December. The situation in other countries of concern is uncertain because of the absence of high-quality surveillance. It is clear, however, that the full epidemiological potential of H5N1 is still unfolding.

Once again, many questions hang in the air. Why has H5N1 failed to reassort? Why have human cases occurred in only two countries? Have cases occurred elsewhere, yet slipped through the surveillance net? Or are the viruses in Thailand and Viet Nam somehow different from those causing outbreaks elsewhere, perhaps intrinsically more apt to infect humans? Although these questions have prompted investigations, no clear answers have as yet emerged. Nor is it known with certainty why H5N1 causes such severe disease in children and young adults, with death frequently following multi-organ failure in addition to severe respiratory disease.

Recent publications have suggested some similarities between H5N1 and the virus responsible for the 1918 pandemic.

The fact that H5N1 has not yet reassorted prompts consideration of the second mechanism by which a pandemic virus can emerge: adaptive mutation. This mechanism involves stepwise changes, which occur as the virus mutates during infection of humans or other mammals, that gradually allow the virus to improve its transmissibility among humans. Adaptive mutation would likely be expressed in a series of independent chains of very limited human-to-human transmission.

The pandemics of 1957 and 1968 are known to have been caused by the exchange of genes between avian and human influenza viruses. The 1918 pandemic, however, is believed by many experts to have begun following adaptive mutation of an avian virus which acquired, following stepwise changes during subsequent human infections, the adaptations needed to sustain efficient human-to-human transmission. Recent publications have suggested other similarities between H5N1 and the 1918 virus in the severity

With the virus now entrenched in rural areas, the rapid elimination of the disease in poultry no longer appears feasible.

of disease, its concentration in the young and healthy, and the occurrence of primary viral pneumonia in the absence of secondary bacterial infection. The present high lethality of H5N1 would probably not be retained in an H5N1-like pandemic virus, as an avian influenza virus is expected to lose pathogenicity when it acquires the improved transmissibility needed to ignite a pandemic. More certain – and more relevant to preparedness planning – is the fact that no virus of the H5 subtype has probably ever circulated among humans, and certainly not within the lifetime of today's world population. Population vulnerability to an H5N1-like pandemic virus would be universal.

No virus of the H5 subtype has probably ever circulated among humans. Population vulnerability to an H5N1-like virus would be universal.

Many experts regard pandemic influenza as the most significant global public health emergency caused by a naturally occurring pathogen. While the timing of this event cannot be predicted, rapid international spread is certain once a virus with the appropriate characteristics emerges. In the previous century, pandemics travelled from continent to continent along sea lanes, with global spread complete within six to eight months. As demonstrated by SARS, spread along the routes of international air travel could shorten this time considerably. The speed of international spread has no direct effect on mortality, but could compromise response capacity should large parts of the world experience almost simultaneous outbreaks. Many of the public health interventions that successfully contained SARS will not be effective against a disease that is far more contagious, has a very short incubation period, and can be transmitted prior to the onset of symptoms.

With the virus now endemic in poultry and expanding its avian and mammalian host range, the objective of averting a pandemic by eliminating further opportunities for human exposure no longer appears feasible. A second opportunity to avert a pandemic could arise if the virus gradually improves its transmissibility among humans through adaptive mutation. Clusters of cases would be indicative, and sensitive surveillance might detect them. It is not known, however, whether rapid intervention with a pandemic vaccine – if available in time – and antiviral drugs – if quantities are sufficient – could successfully interrupt transmission, as this has never been attempted.

The entrenched presence of H5N1 in rural areas and its newfound silent reservoir in apparently healthy domestic ducks greatly

complicate efforts to prevent further human cases. They also create uncertainty about the ability of surveillance systems to provide an early warning at the start of improved human-to-human transmission, should this occur gradually. In the alternative scenario, in which a fully transmissible pandemic virus emerges following a reassortment event, the resulting explosion of cases would be difficult for any surveillance system to miss.

Box 2. **Investigations of human-to-human transmission**

Suspicions that human-to-human transmission may have taken place usually arise when cases occur close together in time and place among persons, such as family members or health care workers, known to have had close contact with a case.

Such clusters of cases have been detected on several occasions during the 2004 outbreaks. All such instances involved family members. To date, no H5N1 cases have been detected in health care workers despite several instances of close, unprotected contact with severely ill patients.

Investigations of human-to-human transmission involve extensive detective work to gather data on individual cases, giving particular attention to dates, times, places, and potential sources of exposure. All possible exposures are considered, systematically evaluated, and gradually narrowed down to the most plausible.

Sources of information range from face-to-face interviews to sampling of animals and environmental areas, to analysis of viruses and hospital records.

Suspicions that human contact was the source of exposure are raised when dates of onset between two cases with close contact fall within the incubation period and no alternative source of exposure appears plausible. In most such investigations, the final conclusion is a judgement call based on the weight of evidence from all available sources.

Whenever possible, viruses are isolated from cases, sequenced, analysed, and compared. For a disease such as avian influenza, the most conclusive evidence would come when two human cases have identical viruses that differ from those circulating in animals. Such a finding literally catches the virus red-handed.

Evidence that a virus has acquired human genes would be an alarming finding, as it suggests reassortment or adaptive mutation towards a more readily transmissible form. At the same time, evidence that a virus remains purely avian does not exclude the possibility that it was transmitted from one human to another, as purely avian H5N1 has amply demonstrated its ability to infect humans.

Table 1. Human cases, Viet Nam

First phase

No.	Sex	Age	Province	Onset	Outcome
1	female	12 years	Ha Nam	25.12.03	died 30.12.03
2	male	10 years	Bac Ninh	29.12.03	died 11.01.04
3	female	30 years	Ha Nam	1.01.04	died 9.01.04
4	male	5 years	Nam Dinh	23.12.03	died 8.01.04
5	female	8 years	Ha Tay	11.01.04	died 17.01.04
6	female	8 years	Ho Chi Minh City	13.01.04	recovered
7	male	13 years	Ho Chi Minh City	14.01.04	died 22.01.04
8	female	23 years	Thai Binh	10.01.04	died 23.01.04
9	female	30 years	Thai Binh	10.01.04	died 23.01.04
10	male	19 years	Bac Giang	11.01.04	recovered
11	female	20 years	Bac Ninh	9.01.04	recovered
12	male	18 years	Lam Dong	25.01.04	died 2.02.04
13	female	16 years	Soc Trang	21.01.04	died 3.02.04
14	female	17 years	Tay Ninh	12.01.04	died 27.01.04
15	female	6 years	Dong Nai	24.01.04	died 3.02.04
16	male	24 years	Lam Dong	29.01.04	died 3.02.04
17	male	23 years	Lam Dong	28.01.04	recovered
18	male	28 years	Binh Phuoc	29.01.04	died 9.02.04
19	male	22 years	Ho Chi Minh City	31.01.04	recovered
20	male	15 years	Thanh Hoa	9.02.04	recovered
21	male	4 years	Lam Dong	5.02.04	died 18.02.04
22	female	16 months	Dong Nai	14.02.04	recovered
23	male	12 years	Tay Ninh	10.03.04	died 15.03.04

Second phase

24	male	4 years	Ha Tay	19.07.04	died 2.08.04
25	female	1 year	Ha Tay	27.07.04	died 4.08.04
26	female	25 years	Hau Giang	31.07.04	died 6.08.04
27	male	14 months	Hanoi	28.08.04[a]	died 5.09.04

Third phase

28	female	16 years	Tay Ninh	24.12.04	died 8.01.05
29	male	6 years	Dong Thap	30.12.04[a]	died 30.12.04
30	male	9 years	Tra Vinh	2.01.05[a]	died 4.01.05
31	female	18 years	Tien Giang	1.01.05	died 19.01.05
32	female	35 years	Tra Vinh	6.01.05	died 17.01.05
33	female	18 years	Hau Giang	1.01.05[a]	died 10.01.05

[a] Date of hospitalization
Average age: 15 years

Table 2. Human cases, Thailand

First phase

No.	Sex	Age	Province	Onset	Outcome
1	male	7 years	Suphanburi	3.01.04	died 3.02.04
2	male	6 years	Kanchanaburi	6.01.04	died 25.01.04
3	male	6 years	Sukhothai	7.01.04	died 27.01.04
4	female	58 years	Suphanburi	19.01.04	died 2.01.04
5	male	6 years	Kanchanaburi	24.01.04	died 2.02.04
6	male	13 years	Chaiyaphum	29.01.04	died 13.02.04
7	male	2 years	Suphanburi	25.01.04	recovered
8	female	27 years	Uttaradit	20.01.04	recovered
9	male	5 years	Khon Kaen	21.01.04	died 3.02.04
10	female	46 years	Lopburi	3.02.04	recovered
11	male	31 years	Nakhon Ratchasima	13.02.04	recovered
12	female	39 years	Ayadhaya/Patumthani[a]	1.03.04	died 12.03.04

Second phase

13	male	18 years	Prachin Buri	31.08.04	died 8.09.04
14	female	32 years	Kamphaeng Phet	16.09.04	recovered
15	female	26 years	Nonthanburi	11.09.04	died 20.09.04
16	female	9 years	Phetchabun	23.09.04	died 3.10.04
17	female	14 years	Sukhothai	8.10.04	died 19.10.04

[a] Patient lived in Ayadhaya but spent her weekends in Patumthani.
Average age: 20 years